

prasugrel-only samples. 918 samples were measured for APTT, of which 172 (18.7%) were reported as >240 seconds, which was the upper limit of quantification. Mean curves of APTT, anti-Xa, and ACT versus time were similar for all treatment arms.

APTT, Anti-Xa, and ACT Baseline Values before Prasugrel / Placebo and UFH / Saline Dosing:

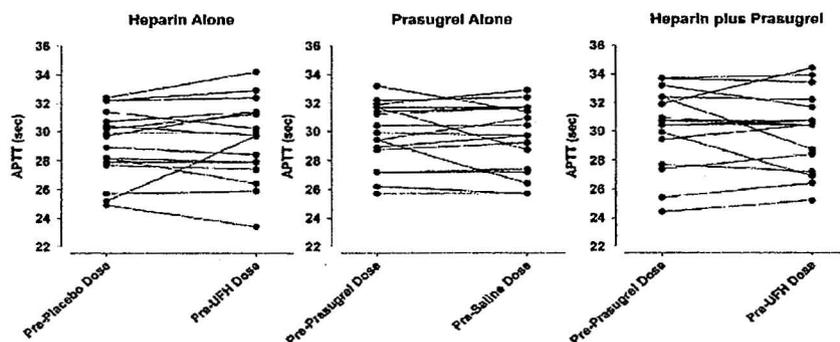


Figure 103 Individual APTT measurements prior to prasugrel / placebo dosing or prior to UFH / saline administration.

Figure 103 presents the individual APTT values for all treatment arms. The panel 1 presents the effect of placebo compared with the basal value of APTT, panel 2 presents the effect of prasugrel compared to basal value of APTT, and panel 3 presents the combined effect of both prasugrel and UFH compared with the basal value of APTT. There is no change in APTT in any of the treatment arms.

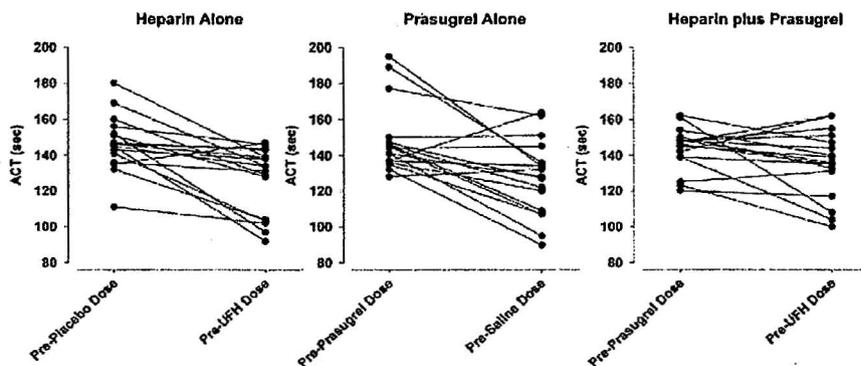


Figure 104 Individual ACT measurements prior to prasugrel / placebo dosing or prior to UFH / saline administration.

Figure 104 presents the individual ACT values for all treatment arms. The panel 1 presents the effect of placebo compared with the basal value of ACT, panel 2 presents the effect prasugrel compared to basal value of ACT, and panel 3 presents the combined effect of both prasugrel and UFH compared with the basal value of ACT. ACT was decreased with the placebo and prasugrel dosing.

Table 120 Statistical comparisons of individual APTT and ACT measurements between prasugrel 2 hours postdose (before UFH / saline dose) and placebo.

Parameter	Geometric Least Squares Means		Ratio of Geometric Least Squares Means (90% CI)
	Prasugrel (pre-UFH/saline)	Placebo	Prasugrel pre-UFH/saline / Placebo
APTT (sec)	29.7	29.5	1.01 (0.994, 1.02)
Anti-Xa (IU/mL)	NC	NC	NC
ACT (sec)	129	140	0.925 (0.883, 0.969)

NC: Not calculated; pre-prasugrel baseline values were below the assay's quantitation limit of 0.06%

Table 120 compares the individual APTT and ACT measurements between samples 2 hours after prasugrel administration that was before UFH or saline dosing and placebo dosing. There is no change in the APTT values for the samples collected 2 hours after prasugrel administration and placebo dosing. There is an increase in the ACT values for samples collected 2 hours after prasugrel administration compared to the placebo arm.

The sponsor has not provided the statistical comparisons in any of the studies related to APTT or ACT. The effect of prasugrel was not compared with the combination of prasugrel with UFH.

Effect of Prasugrel on the APTT, Anti-Xa, and ACT Generated by UFH:

Table 121 Distribution of APTT values above the 240 seconds upper limit of quantification.

Time after UFH dose	Fraction of subjects with APTT >240 seconds ^a	
	UFH alone	Prasugrel + UFH
1	17 / 17	17 / 17
1.5	14 / 17	14 / 17
2	2 / 17	5 / 17
2.5	0 / 17	1 / 17
3	0 / 17	0 / 17

^a Summary does not include Subject 108, who withdrew before receiving UFH.

Table 121 compares the distribution of a number of APTT samples selected more than 240 seconds for all treatment arms. There is no change in the distribution of samples (APTT>250 seconds) collected at 1, 1.5 3 hours for all the treatment arms. There is an increase in the sample number in subjects administered with UFH and prasugrel when compared to subjects administered with UFH alone at 2 and 2.5 hours after UFH dosing.

Figure 105 compares the mean APTT profiles vs time for all treatment arms. There is no change in the APTT values for the samples collected following prasugrel administration alone from 0 to 24 hours. The APTT increased to >240 sec within 15 minutes for the samples administered either with UFH alone or with administration of both UFH and prasugrel, then declined up to the 24 hours time. The AUC_{APTT} values were larger in the UFH + prasugrel arm compared to the UFH arm.

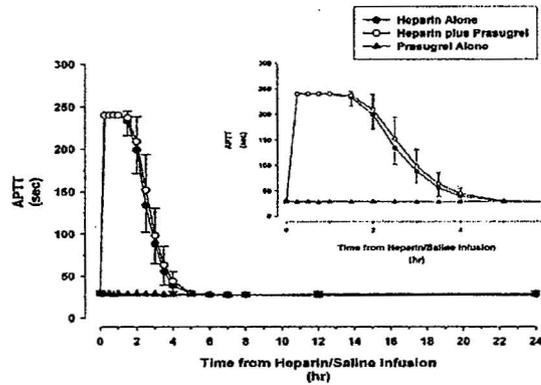


Figure 105 Mean APTT-time profiles following UFH / saline dose.

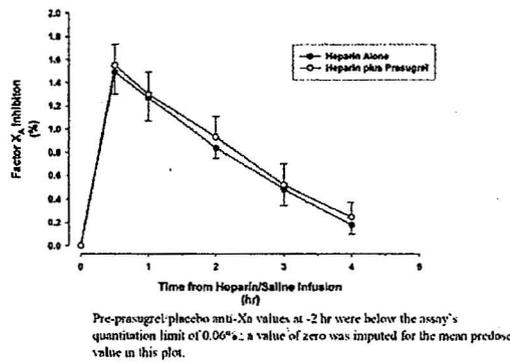


Figure 106 Mean anti-Xa-time profiles following UFH/saline dose.

Figure 106 compare the mean factor-Xa inhibition profiles vs time for all treatment arms. The factor-Xa inhibition reached 1.5% within 30 minutes post dose in both treatment arms. The AUC_{anti-Xa} values were slightly higher in the UFH and prasugrel arm.

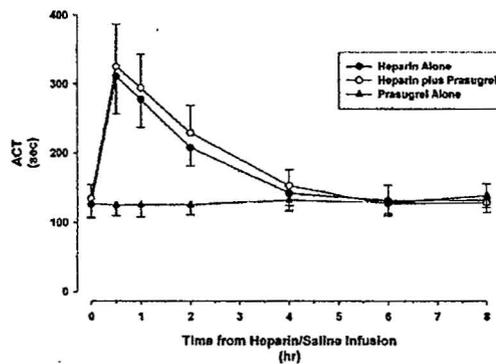


Figure 107 Mean ACT-time profiles following UFH/saline dose.

Figure 107 compares the mean ACT profiles vs time for all treatment arms. Co-administration with prasugrel did not change ACT induced by UFH.

Table 122 Statistical analysis for the coagulation parameters following UFH administration in the presence of prasugrel.

Parameter	Geometric Least Squares Means			Ratio of Geometric Means (90% CI) (Prasugrel + UFH) / (UFH)
	Prasugrel + UFH	UFH	Prasugrel	
AUC _{APTT} (sec × hr)	1237	1207	686	1.02 (0.991, 1.06)
APTT _{15min} (sec)	239	241	28.8	0.992 (0.958, 1.03)
AUC _{Anti-Xa} (IU/mL × hr)	3.34	3.06	NC	1.09 (1.03, 1.16)
Anti-Xa _{30min} (IU/mL)	1.54	1.48	NC	1.04 (0.995, 1.10)
AUC _{ACT} (sec × hr)	1425	1375	1043	1.04 (0.993, 1.08)
ACT _{30min} (sec)	317	310	125	1.02 (0.949, 1.10)

NC = not calculated

Table 122 compares the coagulation parameters like AUC_{APTT}, AUC_{anti-Xa} and AUC_{ACT} for all treatment arms. The ratio of mean prasugrel + UFH treatment with UFH treatment alone for AUC_{APTT}, AUC_{anti-Xa} and AUC_{ACT} were 1.02, 1.09, and 1.04 respectively. Prasugrel has no effect on the APTT, inhibition of factor-Xa and ACT induced by UFH.

Platelet Aggregation Study:

The mean IPA induced by 5 and 20 μM ADP of 81-86% occurred at 1 and 2 hours after the prasugrel dose, prior to UFH administration. The mean IPA induced by 5 and 20 μM ADP decreased to 74% and 75%, respectively at 15 minutes following UFH dosing, no significant difference in IPA after prasugrel and UFH dosing compared to prasugrel alone. No significant difference in IPA after prasugrel and UFH dosing compared to prasugrel alone at 6 and 10 hours post-UFH dose.

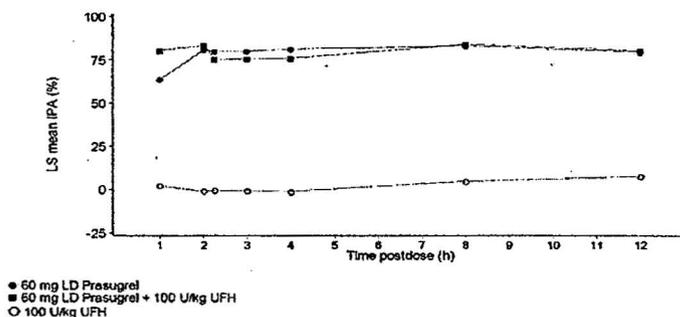


Figure 108 LS mean IPA response to 20 μM ADP time profile following UFH administration in the presence of prasugrel.

Figure 108 compares the IPA profiles vs time to 20 μM ADP for all treatment arms. The IPA to 20 μM was not affected when a 60 mg LD of prasugrel was co-administered with 100 U/kg UFH.

Table 123 compares IPA response to 20 μM ADP obtained in all treatment arms. The difference in the IPA response to 20 μM was not statistically significant when prasugrel was administered alone or with UFH at all time points except at 1 hour following administration of prasugrel.

Table 123 Statistical comparisons of IPA response to 20 µM ADP following UFH administration in the presence of prasugrel.

Time (h) ^a	LS mean IPA (90% CI)			(Prasugrel + UFH)-(prasugrel alone)	
	Prasugrel + UFH (N=17)	Prasugrel alone (N=17)	UFH alone (N=17)	Difference (90% CI)	P-value
1 ^b	80.5 (75.9, 85.0)	63.7 (59.1, 68.2)	2.12 (-2.43, 6.66)	16.8 (10.7, 22.9)	<0.0001
2 ^b	83.2 (78.7, 87.8)	80.8 (76.2, 85.3)	-0.84 (-5.39, 3.70)	2.49 (-3.60, 8.59)	0.4996
2.25	75.3 (70.8, 79.9)	80.1 (75.6, 84.6)	-0.34 (-4.88, 4.20)	-4.76 (-10.9, 1.34)	0.1988
3	75.4 (70.9, 79.9)	80.0 (75.5, 84.6)	-0.56 (-5.11, 3.98)	-4.61 (-10.7, 1.49)	0.2129
4	75.9 (71.3, 80.5)	81.2 (76.6, 85.7)	-1.05 (-5.60, 3.49)	-5.29 (-11.5, 0.887)	0.1585
8	83.9 (79.2, 88.5)	83.0 (78.3, 87.7)	4.82 (0.27, 9.36)	0.886 (-5.38, 7.15)	0.8154
12	80.5 (75.9, 85.0)	79.4 (74.8, 84.1)	7.58 (3.03, 12.1)	1.07 (-5.12, 7.25)	0.7760

^a Time relative to the prasugrel/placebo dose

^b Prior to the UFH/saline dose

Bleeding time:

The co-administration of prasugrel and UFH significantly prolongs the bleeding time at 4 and 6 hours after the prasugrel dose compared to baseline.

Table 124 Statistical comparisons of bleeding time ratio following UFH administration in the presence of prasugrel.

Time (h) ^b	Geometric mean bleeding time ratio (90% CI) ^a			(Prasugrel + UFH)/(prasugrel alone)	
	Prasugrel + UFH (N=17)	Prasugrel alone (N=17)	UFH alone (N=17)	Ratio (90% CI)	P-value
4	3.45 (2.83, 4.22)	2.69 (2.27, 3.21)	1.29 (1.08, 1.53)	1.28 (0.990, 1.66)	0.1134
6	2.87 (2.38, 3.45)	2.47 (2.08, 2.94)	1.13 (0.950, 1.34)	1.16 (0.907, 1.48)	0.3167

^a Bleeding time ratio = bleeding time at time t / bleeding time at baseline (predose)

^b Times are relative to the prasugrel/placebo dose, and are equivalent to 2 and 4 hours after the UFH/saline dose

Table 124 compares the bleeding time ratios for all treatment arms. The bleeding time at 4 and 6 hours post dose was prolonged by 28% and 16% in the prasugrel + UFH arm compared to prasugrel alone. The differences between prasugrel + UFH and UFH alone arms were even higher: 167% and 154% at 4 and 6 hours respectively.

COMMENTS:

- Prasugrel has no effect on the APTT, inhibition of factor-Xa and ACT induced by UFH based on the comparison of parameters like AUC_{APTT}, AUC_{anti-Xa} and AUC_{ACT}. The IPA to 20 µM was not affected in the combination treatment with 60 mg LD of prasugrel and 100 U/kg UFH compared to the treatment with 60 mg LD of prasugrel.
- Although the sponsor reported that the differences in bleeding time ratio between the treatment arms were statistically insignificant, there was about 28% increase in bleeding time ratio at 4 hours post dose of prasugrel with UFH. The differences between prasugrel + UFH and UFH alone arms were even higher: 167% and 154% at 4 and 6 hours respectively.
- Labeling Comment: Since the bleeding time was markedly prolonged when prasugrel was co-administered with heparin, the caution should be exercised when these drugs are co-administered.

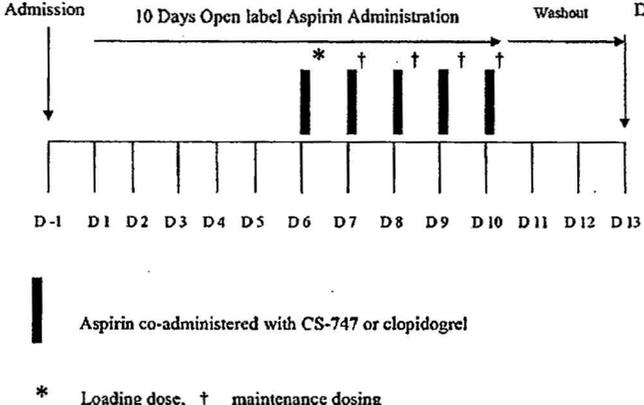
4.2.20 Aspirin Interaction Study With Prasugrel or Clopidogrel in Healthy Subjects (H7T-EW-TAAE)

Principal Investigator: A Wadham, MD, BSc, MSc, MPhil.

Study center: Pharma Bio-Research, Zuidlaren, The Netherlands.

Study period: 13 February 2002 through 15 May 2002.

Phase of development: Phase I

Objectives	<p>Primary: To assess the safety and tolerability of prasugrel when co-administered with aspirin.</p> <p>Secondary: To assess the pharmacodynamic effects (inhibition of platelet aggregation (IPA) and bleeding times) of prasugrel plus aspirin compared to aspirin alone and clopidogrel plus aspirin.</p> <p>To assess the pharmacokinetics of prasugrel metabolites when prasugrel is co-administered with aspirin.</p> <p>To compare results on platelet aggregation obtained by turbidometric platelet aggregation and inhibition of platelet response as measured with a new platelet function analyzer (Accumetrics Ultegra device).</p>
Study Design	<p>This was a single-centre, open-label, randomized, dose escalation study.</p>  <p style="text-align: center;">Admission 10 Days Open label Aspirin Administration Washout Discharge</p> <p style="text-align: center;">D-1 D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13</p> <p style="text-align: center;">* Loading dose, † maintenance dosing</p>
Study Population	Healthy male and female subjects, aged 22 to 60 years, inclusive, for each platelet agonist, (N=34).
Investigational Drug	Prasugrel: 10 mg tablets, lot numbers 01331172, 01331173, 01331174. Aspirin: 325 mg enteric-coated tablets, lot number 1F25A.
Comparator	Clopidogrel: 75 mg tablets, lot number 01I06A.
Dosage and Administration	<p>Aspirin at a daily dose of 325 mg enteric-coated tablets. On Day 6, all subjects were administered a single loading dose (LD) of prasugrel or clopidogrel followed by 4 days of maintenance dosing (MD) in addition to continued aspirin administration.</p> <p>Group 1 received 20 mg LD followed by 5 mg MD of prasugrel.</p> <p>Group 2 received 30 mg LD followed by 7.5 mg MD of prasugrel. Group 3 received 40 mg LD followed by 10 mg MD of prasugrel.</p> <p>Group 4 received 60 mg LD followed by 15 mg MD of prasugrel. Clopidogrel dosed 300 mg LD followed by a MD of 75 mg, in parallel with the four prasugrel groups.</p>

Blood Sampling:	PK: Blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 4, 6, 9 and 12 hours post-dose to prasugrel LD (Day 6), pre-dose (Day 7 to Day 9), pre-dose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 9, 12 and 24 hours post dose to prasugel MD (Day 10). PD, platelet aggregation: predose (Day 1, Day 4, Day 7 to Day 9), predose, 2, 4 and 6 hours postdose (day 5, Day 6, Day 10), and approximately 24, 48, 72, 96, 120 and 144 hours after the last dose on Day 10. PD, bleeding time: predose on Day 1, 4 hours post dose on Day 5, 6, 10, and 24 hours post dose on Day 11.
PD Assessment	Noncompartmental parameter like area under the curve of APTT (AUC_{APTT}), anti-Xa ($AUC_{anti-Xa}$), and ACT (AUC_{ACT}) were calculated from zero to time t, where time zero was time of UFH / saline dose and time t was last time point (WinNonlin).
Statistical methods	Effects due to various dosing regimens of prasugrel and clopidogrel on percent inhibition of MPA (IPA) and Ivy bleeding time (BT) were assessed using linear mixed effects analysis of covariance. These statistical analyses were carried out using SAS Version 8.2.

Results

Demographics:

A total of 34 healthy male and female subjects, aged 18 to 60 years with body mass index (BMI) between 19-29 kg/m², inclusive.

Assay:

The figure of platelet aggregation from pre and post administration of thienopyridine was presented in TAAU review. After ADP addition, light transmission / aggregation increases due to the platelet aggregation that is recorded. Maximal platelet aggregation is defined as the maximum aggregation (increase in the light transmission) seen during the monitoring period. Residual platelet aggregation is the percent aggregation presented after 6 minutes following addition of ADP.

Pharmacodynamics:

Platelet Aggregation Study:

The mean IPA response to 20 μM ADP resulted in a dose dependant effect following administration with 20 mg LD / 5 mg MD, 30 mg LD / 7.5 mg MD, 40 mg LD / 10 mg MD and 60 mg LD / 15 mg MD prasugrel at the end of the aspirin phase.

Figure 109 compares the IPA response vs. time to 20 μM ADP in four treatment arms at the end of the aspirin phase. The IPA response to 20 μM ADP was dose dependent. The IPA response to 20 μM ADP following prasugrel without the aspirin administration was not studied as a comparative profile.

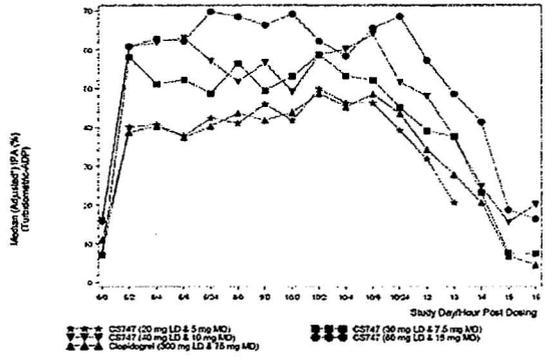


Figure 109 IPA response adjusted for the baseline MPA at the end of aspirin phase.

The figure below shows the distribution of IPA on Day 6 and 24 hours post maintenance dose. The highest inhibition of platelet aggregation was achieved in the group, who received 60/10 mg doses of prasugrel,

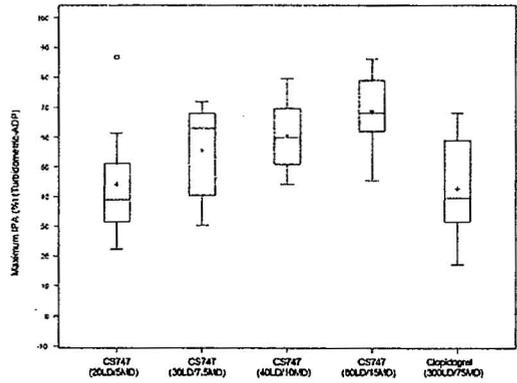


Figure 110 Distribution of maximum IPAs on Day 6 (ADP), with the outliers (indicated by the small open boxes), minimum, lower quartile, median, mean (indicated by a plus sign), and maximum.

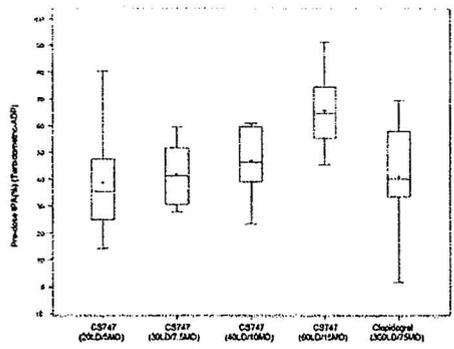


Figure 111 Distribution of IPAs at 24 hours post-maintenance on Day 10 (ADP), with minimum, lower quartile, median, mean (indicated by a plus sign), and maximum.

Bleeding time:

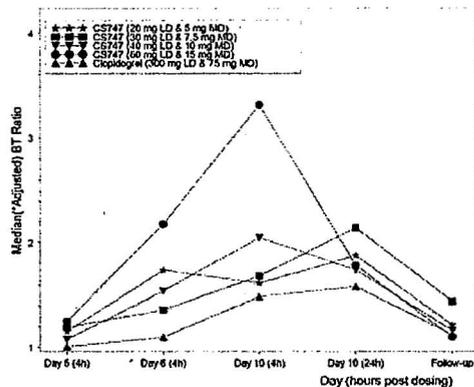


Figure 112 Time profiles of the predicted median bleeding time ratios.

The figure below compares the bleeding time ratios in four treatment arms at 4 hours post dose on Day 5, 6, and 10, and 24 hours post dose on Day 10. The bleeding time following prasugrel without aspirin administration was not studied as a comparative profile.

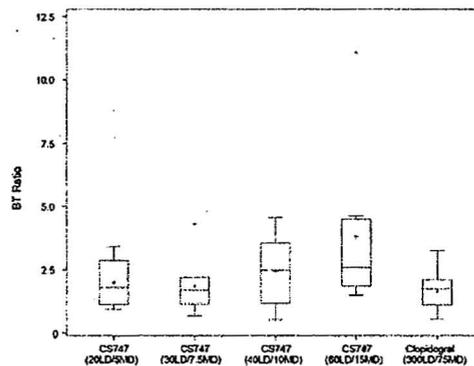


Figure 113 Distribution of bleeding time ratios by treatment group on Day 10, 4 hours post-dose.

COMMENTS:

1. The sponsor compared safety and tolerability of four different regimens of LD and MD of prasugrel co-administrated with a 325 mg daily dose of aspirin. The highest IPA response as well as a prolongation of bleeding time was reported in the group of subjects who received a 60 mg LD and 10 mg MD of prasugrel.
2. The sponsor presented the pharmacokinetics of prasugrel inactive metabolites but not the active metabolite. The effect of aspirin coadministration on the pharmacokinetics of the active metabolite of prasugrel is not known.
3. The bleeding time ratio was the highest in the group who received a 60/10 mg of prasugrel.

4.2.21 Assess the Pharmacodynamic Interaction between Aspirin and Prasugrel in Healthy Subjects (H7T-EW-TAAU)

Principal Investigators: Drs. C Mills, W Malyszczak and J Chiesa.

Study center: Veeda Clinical Research Ltd., Old Convent of Notre Dame, 119 Looseleigh Lane, Derriford, Plymouth, PL6 5HH, UK.

Study period: 9 January 2006 to 21 April 2006

Phase of development: Phase I

Objectives	<p>Primary: To assess the pharmacodynamic interaction between aspirin and prasugrel: inhibition of platelet aggregation (% IPA) by 20 μM adenosine diphosphate (ADP) after a 60 mg loading dose (LD) and a 10 mg maintenance dose (MD) of prasugrel in combination with a daily dose of 150 mg aspirin.</p> <p>Secondary: To assess the pharmacodynamic interaction between a single 900 mg aspirin dose and daily 150 mg aspirin with 10-mg prasugrel MD.</p> <p>To assess the pharmacodynamic interaction between aspirin and prasugrel in terms of % IPA to 5 μM ADP, collagen and arachidonic acid.</p> <p>To assess the safety and tolerability of aspirin and prasugrel given alone and in combination.</p> <p>To evaluate the response of the vasoactive-stimulatory phosphoprotein (VASP) assay after doses of prasugrel and aspirin.</p> <p>To conduct exploratory analyses of aspirin resistance defined by thromboxane B2 (TxB2) concentrations.</p>
Study Design	<p>This was an open label, fixed sequence, two-period, two-treatment crossover study.</p> <p>Legend:</p> <ul style="list-style-type: none"> ↓ 60 mg Prasugrel ◆ 150 mg Aspirin (once a day) █ Study Residential Period ★ Washout between Treatment Periods (Subjects will be required to attend the CRU on Days 12-14 on an outpatient basis following Treatment A for the assessment of inhibition of platelet aggregation) ↓ 10 mg Prasugrel ⊕ 900 mg Aspirin (single dose)
Study Population	Healthy male and female subjects, aged 18 to 53 years, inclusive (N=23)
Investigational Drug	Prasugrel: 10 mg tablets, lot number CT523627. Aspirin: 75 mg and 300 mg enteric coated tablets, lot numbers BN 62616 and BN60667 respectively.
Dosage and Administration	<p>Treatment 1: Single oral 60 mg prasugrel on Day 1, followed by 7 days of 10-mg MD (Days 2 to 8).</p> <p>Treatment 2: A daily dose of 150 mg for 14 days (Days -5 to 9), co-administered with 60 mg prasugrel LD on Day 1, and a 10 mg prasugrel MD from Day 2 to 9. A single 900 mg aspirin administered 2 hours after chronic</p>

	aspirin and prasugrel dosing on Day 9 (last day).
Blood Sampling:	<p>PD, platelet aggregation: predose, 1, 2, 4 and 24 hours postdose on Days 1 and 8 (for 5 and 20 μM ADP, 2 μg/mL collagen and 1.5 mM arachidonic acid) and at 96, 120 and 144 hours postdose on Day 8 (for 5 and 20 μM ADP only) during Treatment 1. Pre aspirin dose on Day -5, 2 hours post aspirin dose on Day -1, predose, 1, 2, 4 and 24 hours post prasugrel dose on Day 1, predose, 1, 2, 4, 6 and 24 hours postdose on Day 8, and at 2 (before the single acute 900-mg aspirin dose), 4, 6 and 24 hours postdose on Day 9.</p> <p>PD, VASP phosphorylation: predose, 2, 4 and 24 hours postdose on Day 1, and predose and 4 hours postdose on Day 8.</p> <p>PD, serum TxB2 concentrations: Pre aspirin dose on Day -5, 4 hours post aspirin dose on Day -1, 4 hours after the prasugrel LD on Day 1 and 4 hours after co-administration of aspirin and prasugrel on Day 8.</p>
Assay	<p>Platelet aggregation in platelet rich plasma was measured using turbidometric method with 5 and 20 μM ADP, 2 μg/mL collagen and 1.5 mM arachidonic acid as the agonists.</p> <p>VASP phosphorylation was measured by whole blood flow cytometric assay using a Biocytex Platelet VASP kit. The assay reported the ratio of non-phosphorylated VASP to phosphorylated VASP as platelet reactivity index (PRI) in percentage units.</p> <p>Serum TxB2 was measured using an enzyme immunoassay (EIA) procedure</p>
Statistical methods	<p>Pharmacodynamic parameters including platelet aggregation induced by ADP, collagen and arachidonic acid, and VASP were analyzed separately by mixed-effect models. Least squares (LS) mean differences, 90% CI and corresponding p-values were calculated for comparisons between prasugrel administered alone and prasugrel coadministered with aspirin. Pearson and intra-class correlation coefficients were calculated to assess the relationship between VASP and platelet aggregation assessed by maximum platelet aggregation (MPA) to ADP. Log-transformed bleeding time data were analyzed by a mixed-effects model. Geometric LS mean ratio of bleeding time, 90% CI and corresponding p-values were calculated for the comparisons between prasugrel administered alone and prasugrel coadministered with aspirin. In addition, bleeding time data following a single acute 900-mg aspirin dose on Day 9 were compared with data on Day 8 when prasugrel was coadministered with 150 mg aspirin.</p>

b(4)

Results

Demographics:

A total of 23 healthy male Caucasian subjects, aged 18 to 53 years, inclusive, participated in the study. Summary of demographics is presented in the following table.

Table 125 Subject Demographics

Subject Number	Age (years)	Body Weight (kg)	Height (cm)	BMI (kg/m ²)
1	24	83.6	182	25.2
2	23	104.2	190	28.9
3	19	97.4	193	26.1
4	18	81.1	177	25.9
5	23	66.2	180	20.4
6	19	78.0	171	26.7
7	40	75.7	179	23.6
8	47	71.7	175	23.4
9	30	88.2	186	25.5
10	24	94.1	179	29.4
11	26	75.8	176	24.5
12	21	74.5	177	23.8
13	52	61.8	179	19.3
14	27	91.0	187	26.0
15	40	66.6	170	23.0
16	24	84.3	178	26.6
17	24	78.9	184	23.3
18	53	83.4	183	24.9
19	23	68.5	181	20.9
20	22	85.2	188	24.1
21	21	78.8	179	24.6
22	23	66.9	170	23.1
23	37	93.6	187	26.8
Mean (SD)	29 (11)	80.4 (11.0)	180 (6)	24.6 (2.4)

Assay:

Figure 114 represents aggregation tracings from pre and post administration of thienopyridine. After ADP addition, light transmission / aggregation increases due to the platelet aggregation that is recorded. Maximal platelet aggregation is defined as the maximum aggregation (increase in the light transmission) seen during the monitoring period. Residual platelet aggregation is the percent aggregation presented after 6 minutes following addition of ADP.

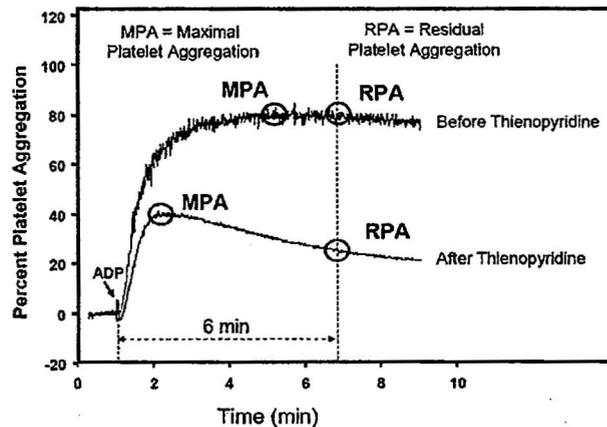


Figure 114 Light transmission aggregation tracings from pre and post administration of a thienopyridine.